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PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WPP80673		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/01857	15/05/2000	13/05/1999
International Patent Classification (IPC) or national classification and IPC A61K31/495		
Applicant PHARMA MAR S.A et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/12/2000	23.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Young, A Telephone No. +49 89 2399 7811

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01857

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-22 as originally filed

Claims, No.:

1-11 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 3-11.

because:

☒ the said international application, or the said claims Nos. 3-11 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1, 3-11

	No:	Claims	2
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1 and 2
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Concerning Section III:

Claims 3 -11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Concerning Section V:

The following documents mentioned in the search report are considered as being the relevant state of the art.

D1: US-A-5 256 663 (SAKAI RYUICHI ET AL) 26 October 1993 (1993-10-26)

D2: US-A-5 478 932 (SAKAI RYUICHI ET AL) 26 December 1995 (1995-12-26)

D3: IZBICKA: 'In vitro antitumor actitivity of the novel marine agent, Ecteinascidin-743 (ET-743, NSC-648766) against human tumors explanted from patients ' ANNALS OF ONCOLOGY, vol. 9, no. 9, 1998, pages 981- 987, XP000900662

D4: ' Ecteinascidin-743 ' DRUGS OF THE FUTURE, vol. 22, no. 11, 1997, page 1279 XP002145352

D5: GIAVAZZI: ' Ecteinascidin-743, a New Marine Natural Product with Potent Antitumor Activity ' CLINICAL CANCER RESEARCH, vol. 4, no. 8, 1998, pages 1977-1983, XP000930036

Document D1 refers to a pharmaceutical composition containing ET 743 and to the use of such a composition as antitumor agent (see column 19 line 9 to column 20 line 15 and claims 1-4). Document D2 describes the use of ecteinascidins, explicitly ET 743 to protect mice in vivo against several tumors (see column 1, line 40 - column 2 line 12) including ovarian sarcoma, melanoma and Lewis lung carcinoma. Document D3 shows the antitumor activity of ET 743 against human tumors explanted from patient e.g. breast cancer and sarcoma (see table 1b, page 984). The data indicates (see page 985 last paragraph to page 986 first paragraph), that ET 743 may be used to treat cancer resistant to other agents. Document D4 discloses the antitumor effect of ET 743 (0.05, 0.1 and 0.2 mg/kg i.v. every 4 days x 3) in nude mice transplanted s.c. with human ovarian carcinoma xenografts. Document D5 refers to the potent antitumor effect of ET 743, and indicates its use in DDP-refractory tumors. (see page 1980 table 1-3, and page 1982 paragraph 2)

The invention refers to the use of ET 743 for the treatment of cancer in a human

patient. The route of administration is intravenous infusion. The cancer is selected from sarcoma, soft tissue sarcoma, bone sarcoma or breast cancer and may be metastatic or resistant/refractory to other treatment. Also a preferred scheme of dosage is disclosed.
Claim 1 is in a second medical use format and therefore bound to the use of treating cancer. Claim 2 is a composition claim for any pharmaceutical use. Claims 3-11 are method of treatment claims. From the prior art the antitumor effect of ET 743 is very well known. D1 discloses a pharmaceutical composition comprising Et 743.
Therefore claim 2 is not new in the sense of Article 33(2)PCT.
The problem to be solved by the present invention is to provide a method of treating cancer in a human patient. The posed solution is the use of ET 743. From all prior art documents the antitumor effect of ET 743 is known. D3 discloses a variety of human tumors including sarcoma and breast cancer and the activity of ET 743 against this tumors. Also that ET 743 may be useful for the treatment of cancer resistant to other agents is mentioned in D3 and D5. Although all the data is from in vitro or in vivo trials in mice the authors suggest a potent antitumor effect of ET 743 in a human patient. Thus, claims 1-11 lack inventive step according to Article 33(3)PCT.

For the assessment of the present claims 1 and 3-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatmeant.

Concerning Section VI:
Certain published documents (Rule 70.10)

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US99/07471	14 October 1999	5 April 1999	6 April 1998
US 99/10233	18 November 1999	11 May 1999	11 May 1998